UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/384,959	08/27/1999	RAM SASISEKHARAN	M065b 7046H0	8533

26161 7590 02/25/2003

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	27

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/384,959	SASISEKHARAN ET AL.
Examiner	**Art Unit**
Richard G Hutson	1652

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-34 and 46-49* is/are pending in the application.

4a) Of the above claim(s) *32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *30,31,33,34 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/27/2002 has been entered.

Applicants amendment of claim 30 and 46 and cancellation of claims 1-29, 35-45 and 50-57, Paper No. 23, 11/27/2002, is acknowledged. Applicants' arguments filed on 11/27/20029, Paper No. 23, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 30-34, and 46-49 are at issue and are present for examination.

Claim 32 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Applicants comments with respect to claim 32 are acknowledged.

Claim Objections

Claims 30, 46 and 49 remain objected to because of the following informalities:

Claims 30 and 46 each are drawn to a method of using a heparinase selected from a number of different heparinases. The format that the claims appear in remains confusing and unclear. It is suggested that in order to make the claims clearer, the "colon" after "comprising" be deleted. This objection was stated in the previous office action, and rather then "move" the referred to colon, applicants "added" a colon where they were instructed to "move" a colon to. Thus it is now suggested that applicants "delete" the original colon, as a means of coming to the same end.

Claim 49 is dependent on rejected claim 46.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30, 31, 33, 34 and 46-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 30 (31, 33, and 34 dependent on) and 46 (47-49 dependent on) are indefinite in the recitation of "having a modified product profile, wherein the modified product profile of the modified heparinase II is at least 10% different than a native product profile of a native heparinase II," as the specification fails to teach which what the product profile of a native heparinase II is and how one determines or what a product profile is that is 10% different from such a native product profile. While page

20, lines 21-32, discuss applicants intent as to a "modified product profile", it remains unclear how one would determine a product profile that is 10% different and thus the metes and bounds of the genus of those methods of using a modified heparinases are unclear.

Claims 30 (31, 33, and 34 dependent on) and 46(47-49 dependent on) are further indefinite in the recitation of " a native product profile of a native heparinase II". Is a native product profile of a native heparinase II different than a product profile of a heparinase II? The product profile of a native heparinase II is dependent on many variables associated with the enzymatic reaction. The product profile for a native heparinase II will be different depending on the conditions at which the product profile is determined (i.e. substrates, buffers, salts present and their concentration etc...). Thus the above recitation is unclear.

Claims 30 (31, 33, and 34 dependent on) and 46 (47-49 dependent on) are indefinite in that it is unclear what applicants consider to be encompassed by a "modified heparinase". At what point is a heparinase become a modified heparinase, and what distinguishes a modified heparinase I, from a modified heparinase II, from a modified heparinase III? As it is unclear when a heparinase becomes a modified heparinase and when a modified heparinase becomes a different modified heparinase, more weight is given to the additional structural limitations of the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 33, 34, 46, 47 and 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was originally stated in the previous office action, Paper No. 14, 9/11/2001, applicants traversed in Paper No. 17, 3/25/2002, and the rejection was maintained in the following action, Paper No. 19, 6/21/2002. In response to the previous rejection applicants have amended independent claims 30 and 46 and traverse the rejection based on these amendments.

Applicants have amended the claims such that the claimed methods are limited to the use of modified heparinases that contain at least one amino acid residue that has been substituted with a different amino acid residue selected from those residues which correspond to a cysteine at position 348, a histidine at position 238, 252, 347, 440, 451 and 579 and a residue at positions 446-451 of SEQ ID NO: 2 (modified heparinase II). Applicants continue to traverse this rejection on the basis that the disclosure of the amino acid residues that play a role in the enzymatic and binding activity of heparinase II along with a number of described species is sufficient to demonstrate applicants were in possession of the claimed invention.

Applicants argument is not found persuasive, because while applicants have identified certain amino acid residues important in the catalytic and binding activity of

heparinase II, this information in combination with the limited number of described species is insufficient to describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention. Applicant is reminded that the claimed heparinase variants include all modified heparinase enzymes having substitutions corresponding to those residues indicated in the claims. The claimed genus remains inadequately described with respect to the particular structure to function/activity relationship disclosed for the taught species and the genus claimed. It is the combination of applicants claimed genus of all modified heparinases with the corresponding substitutions as well as the functional limitation that the claimed mutants have a modified product profile that is at least 10% different than a native product profile of a native heparinase II (See also above 112 2nd paragraph rejection) or a the claimed mutants have a k_{cat} value that is at least 10% different than a native heparinase II k_{cat} value, that results in the claimed genus being inadequately described.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 30, 33, 34, 46, 47 and 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for those methods of cleaving a heparin-like or heparan sulfate-like glycosaminoglycan comprising contacting said heparin-like or heparan sulfate-like glycosaminoglycan with a modified heparinase

II comprising SEQ ID NO: 2 with a specific substitution at histidine 440 or cysteine 348, does not reasonably provide enablement for those methods of cleaving a heparin-like or heparan sulfate-like glycosaminoglycan comprising contacting said heparin-like or heparan sulfate-like glycosaminoglycan with any modified heparinase having a modified product profile or heparinase k_{cat} that is at least 10% different than the native heparinase II, wherein said modified heparinase contains at least one amino acid residue that has been substituted with a different amino acid residue selected from those residues which correspond to a cysteine at position 348, a histidine at position 238, 252, 347, 440, 451 and 579 and any residue at positions 446-451 of SEQ ID NO: 2 (modified heparinase II). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection was originally stated in the previous office action, Paper No. 14, 9/11/2001, applicants traversed in Paper No. 17, 3/25/2002, and the rejection was maintained in the following action, Paper No. 19, 6/21/2002. In response to the previous rejection applicants have amended independent claims 30 and 46 and traverse the rejection based on these amendments.

Applicants have amended the claims such that the claimed methods are limited to the use of modified heparinases that contain at least one amino acid residue that has been substituted with a different amino acid residue selected from those residues which correspond to a cysteine at position 348, a histidine at position 238, 252, 347, 440, 451 and 579 and a residue at positions 446-451 of SEQ ID NO: 2 (modified heparinase II)

and a serine residue at position 377 of SEQ ID NO: 4 (modified heparinase I). Applicants continue to traverse this rejection on the basis that the claims provide a set of residues that can be modified to produce molecules with altered activity and the recitation of these residues in combination with teachings of the disclosure and extensive working examples provides adequate guidance to one of skill in the art to produce a modified molecule with the desired activity.

This is not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants as claimed by applicants (i.e., with the claimed functional limitations (See above 112 2nd paragraph rejection) and the claimed structural limitations) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

As discussed above under 112 1st paragraph written description, applicant is reminded that the claimed heparinase variant methods include the use of all modified heparinase enzymes having substitutions corresponding to those residues indicated in the claims. The claimed genus remains inadequately enabled with respect to the

particular structure to function/activity relationship disclosed for the taught species and the genus claimed. It is the combination of applicants claimed genus of all modified heparinases with the corresponding substitutions, as well as the functional limitation that the claimed mutants have a modified product profile that is at least 10% different than a native product profile of a native heparinase II (See also above 112 2nd paragraph rejection) or the claimed mutants have a k_{cat} value that is at least 10% different than a native heparinase II k_{cat} value, that results in the claimed genus not being enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 30, 33, 46 and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Su et al. (U.S. Patent No: 5,681,733, filed 6/10/1994).

The rejection was originally stated in the previous office action, Paper No. 14, 9/11/2001, applicants traversed in Paper No. 17, 3/25/2002, and the rejection was maintained in the following action, Paper No. 19, 6/21/2002. In response to the previous rejection applicants have amended independent claims 30 and 46 and traverse the rejection based on these amendments.

Applicants traverse this rejection on the basis that the claims as amended are not anticipated by the teachings of Su et al. because the modified heparinase II enzymes in the claimed methods require that at least one of a list of specific amino acid residues is modified compared to a native heparinase II and that these modified heparinase II molecules do not include native heparinase I, II or III. As discussed above under 112 2nd paragraph rejection, it is unclear what applicants intend to be encompassed by a "modified heparinase". Thus the use of the heparinase III taught by Su et al., which does not have a cysteine at the corresponding position 348 of SEQ ID NO: 2 is to be encompassed by a modified heparinase II and thus the taught methods are considered to anticipate the rejected claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 34 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Su et al. (U.S. Patent No: 5,681,733, filed 6/10/1994) as applied to Claims 30, 33, 46 and 47 above, and further in view of Langer et al. (U.S. Patent No. 4,373,023, issued 2/8/1983).

The rejection was originally stated in the previous office action, Paper No. 14, 9/11/2001, applicants traversed in Paper No. 17, 3/25/2002, and the rejection was

maintained in the following action, Paper No. 19, 6/21/2002. In response to the previous rejection applicants have amended independent claims 30 and 46 and traverse the rejection based on these amendments.

Applicants traverse this rejection as the above 102 rejection over Su et al. on the basis that Su et al. does not describe the claimed modified heparinase II molecules on the basis that the claims require that at least one of a list of specific amino acid residues must be modified compared to a native heparinase II. As above, this argument is not found persuasive because the heparinase III as taught by Su et al. does not have a cysteine at the corresponding position 348 of SEQ ID NO: 2 and thus the taught heparinase III is considered to be encompassed by a "modified heparinase II" and thus the methods remain obvious over Su et al. and Langer et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapy Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
February 24, 2003